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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,674	02/14/2002	Kenneth K. Sokoll	1004263.156US (1151-4172)	1691

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
03/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/076,674	SOKOLL, KENNETH K.	
	Examiner	Art Unit	
	EMILY M. LE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,12,13,18,19 and 76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-9, 12-13, 18-19 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/05/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 2-3, 10-11, 14-17 and 20-75 are cancelled. Claim 76 is added. Claims 1, 4-9, 12-13, 18-19 and 76 are pending and under examination.

Information Disclosure Statement

2. Part of the information disclosure statement filed 03/05/2010 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Specifically, the cited non patent literatures fails to comply with 37 CFR 1.98 (b)(5), which requires that each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 4-9, 12-13, 18-19 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al.[1] in view of Ladd et al.,[2] as evidenced by result no. 1 of the rng and result no. 1 of the rag search summary pages, as evidenced by Morris et al.[3]

The claims are directed at composition that is a microparticulate comprising a cationic peptide immunogen and an anionic CpG oligonucleotide. The claims require the peptide immunogen to comprise a target B cell antigen or a CTL epitope and a T helper cell epitope; have a net positive charge at a pH in the range of 5.0 to 8.0, which is calculated by assigning a +1 charge for each lysine, arginine and histidine; a -1 charge for each aspartic acid and glutamic acid; and a charge of 0 for all other amino acids in the cationic peptide immunogen. The claims require the anionic CpG oligonucleotide have a net negative charge at a pH in the range of 5.0 to 8.0; and be single-stranded DNA comprising 8 to 64 nucleotide bases with a repeat of a cytosine-guanidine motif, wherein the number of repeats of the CpG motif is in the range of 1 to 10. Additionally, the claims require the cationic peptide immunogen: CpG oligonucleotide charge ratio be in the range of 8:1 to 1:2. Claim 4, which depends on claim 1, requires the cationic peptide immunogen be a mixture of synthetic peptide immunogens. Claim 5, which depends on claim 1, requires the net positive charge of the synthetic peptide immunogen be at least +2. Claim 6, which further limits claim 4,

[1] Krieg et al. WO 01/22972.
[2] Ladd et al. WO 94/25060.
[3] Morris et al. A novel potent strategy for gene delivery using a single peptide vector as a carrier. Nucleic Acid Research, 1999, Vol. 27, No. 17, 3510-3517.

requires the average net positive charge of the mixture of synthetic peptide immunogen to be at least +2. Claim 7, which depends on claims 5 and 6, in the alternative, requires the net negative charge of the anionic oligonucleotide be at least –2. Claim 8, which depends on claim 1, further requires the CPG oligonucleotide to be 18-48 nucleic acids residues in length, and have 3 to 8 repeats of a cytosine-guanidine motif. Claim 9, which depends on claim 1, requires the CpG oligonucleotide to have the formula: 5'X^1CGX^2 3', wherein X^1 is selected from the group consisting of A (adenine), G (guanine) and T (thymine); and X^2 is selected from the group consisting of C (cytosine) and T (thymine). Claim 12, which further limits claim 1, and claim 13, which depends on claim 12, specify that the nucleic acid sequence of the CpG oligonucleotide is SEQ ID NO: 1. Claim 18, which depends on claim 12, requires the cationic peptide immunogen be a synthetic peptide that is conjugated to a T helper cell epitope. Claim 19, which depends on claim 18, specifies that the amino acid sequence of the cationic peptide immunogen is SEQ ID NO: 9. Claim 76, which depends on claim 1, requires the cationic peptide immunogen: CpG oligonucleotide charge ratio be in the range of 4:1 to 1:1.

Prior to the obviousness analysis, the following is observed: The nucleic acid sequence of SEQ ID NO: 1 is 5'TCGTCGTTTTGTCGTTTTGTCGTTTTGTCGTT-3', which is a single stranded DNA of 32 nucleic acid residues in length having 5 repeats of a cytosine-guanidine motif, and has a net negative charge of –32 at a pH in the range of 5.0-8.0. The charge calculation made for SEQ ID NO: 1 is in accordance with Applicant's specification, which provides that the net negative charge on the oligomer or polymer is calculated by assigning a -1 charge for each phosphodiester or

phosphorothioate group in the oligomer. In the instant, the number of cytosine-guanidine repeats is with the range that is instantly claimed, 1-10 and to 3-8. The number of nucleotide bases present in SEQ ID NO: 1 is within the 8-64 and 18-48 ranges set forth in the claims. SEQ ID NO: 1 is also in agreement with the formula 5'X^1CGX^2 3', wherein X^1 is selected from the group consisting of A (adenine), G (guanine) and T (thymine), and X^2 is selected from the group consisting of C (cytosine) and T (thymine). And SEQ ID NO: 1 has a net negative charge of at least –2, as required by the claims.

SEQ ID NO: 9 is a cationic peptide immunogen comprising a CTL epitope and a T helper cell epitope, has a net positive charge of +4, and is synthetic peptide immunogen conjugated to a T-helper epitope. The charge calculation made for SEQ ID NO: 9 is in accordance with Applicant's specification.

On January 06, 2010, The Board of Patents Appeals and Interferences affirmed the rejection of the base invention encompassed by claims 1, 4-9, 12-13, 18-19 and 76. At the time of the decision by the Board of Patents Appeals and Interferences was made, the following limitations: the cationic peptide immunogen:CpG oligonucleotide charge ratio be in the range of 8:1 to 1:2--as recited in independent claim 1, and later limited to the ratio range of 4:1 and 1:1 by newly added claim 76 were not presented for review by the Board of Patents Appeals and Interferences nor was it presented for examination on the merits. The note charge ratio limitation is newly added to the base invention and submitted with the filing of a Request for Continued Examination on 03/05/2010. Hence, the instant rejection is based on the rejection made on the record

for the base invention, and affirmed by the Board of Patents Appeals and Interferences, with the newly added limitations addressed accordingly.

As noted in the rejection, Krieg et al. teaches a composition comprising an immunostimulatory nucleic acid having SEQ ID NO: 429 and an anti-cancer therapy, including immunotherapeutic agent. While it is not readily apparent if the immunotherapeutic agents that Krieg et al. teaches are cationic peptide immunogens comprising a CLT epitope and a T helper cell epitope. However, Ladd et al. teaches an immunotherapeutic agent that is a cationic peptide immunogen comprising a CLT epitope and a T helper cell epitope. Ladd et al. refers to this cationic peptide immunogen as SEQ ID NO: 35. SEQ ID NO: 35 is 100% identical to SEQ ID NO: 9 set forth in the claim. [See result no. 1 of the rag search summary page.]

In the instant case, Krieg et al. discloses that SEQ ID NO: 429 has immunostimulatory activities and to be used as an adjuvant with immunotherapeutic agent. Ladd et al. teaches that the immunotherapeutic agent having SEQ ID NO: 35 is useful for regulating infertility and for treating prostatic hyperplasia, androgen-dependent carcinoma, prostatic carcinoma and testicular carcinoma in males. Ladd et al. also teaches that the cationic peptide immunogen is useful for treating endometriosis, benign uterine tumors, recurrent functional ovarian cysts and premenstrual syndrome, and preventing or treatment of estrogen-dependent breast cancer in females. [Abstract]

The Board of Patents Appeals and Interferences agrees with the Examiner that the based invention is obvious over the teachings of Krieg et al. and Ladd et al.

Directing at the newly added limitations, neither Krieg et al. nor Ladd et al. teaches the claimed charge ratio. However, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to vary the amount/concentration of the immunostimulatory nucleic acid and/or the immunogenic peptide in a composition comprising both active ingredients. Varying the amount of the active ingredients present in the composition would necessarily result in a change of the charge ratio since it is well established that, as evidenced by Morris et al., charge ratio is a function of concentration. Morris et al. teaches varying the concentration of a cationic peptide in the presence of a set amount of anionic DNA to vary the charge ratio of the active ingredients. [Stability and DNase I protection assays, page 3511, in particular.] Hence, it would have been prima facie obvious for one of ordinary skill in the art to vary the amount of immunostimulatory nucleic acid and/or the amount of the immunotherapeutic agent, including amounts that renders a charge ratio range of 8:1 to 1:2. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to vary and/or optimize the function and/or effects of each of the active ingredients in the composition. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the determination of a workable or optimal range is routinely practiced in the art.

As presented to and affirmed by the Board of Patents Appeals and Interferences, Krieg et al. teaches a composition comprising an immunostimulatory nucleic acid and an anti-cancer therapy. [See claim 99] One of the immunostimulatory nucleic acid

Krieg et al. teaches is an anionic CpG oligonucleotide. The anionic CpG oligonucleotide that Krieg et al. teaches has the sequence set forth in SEQ ID NO: 429. [Claim 101, and item 429 on page 46.] SEQ ID NO: 429 of Krieg et al. is 100% identical to the SEQ ID NO: 1 set forth in the claims. [See result no. 1 of the rng search summary page.] Thus, SEQ ID NO 429 of Krieg et al. is a single stranded DNA of 32 nucleic acid residues in length having 5 repeats of a cytosine-guanidine motif, and has a net negative charge of –32 at a pH in the range of 5.0-8.0. In the instant, the number of cytosine-guanidine repeats is with the range that is instantly claimed, 1-10 and to 3-8. The number of nucleotide bases present in SEQ ID NO: 429 of Krieg et al. is within the 8-64 and 18-48 ranges set forth in the claims. SEQ ID NO: 429 of Krieg et al. is also in agreement with the formula 5'X^1CGX^2 3', wherein X^1 is selected from the group consisting of A (adenine), G (guanine) and T (thymine), and X^2 is selected from the group consisting of C (cytosine) and T (thymine). And SEQ ID NO: 429 of Krieg et al. has a net negative charge of at least –2.

And by anti-cancer therapy, Krieg et al. intends to encompass immunotherapeutic agents. [Lines 1-4 of page 15] In the instant, it is not readily apparent if the immunotherapeutic agents that Krieg et al. teaches are cationic peptide immunogens comprising a CLT epitope and a T helper cell epitope. However, Ladd et al. teaches an immunotherapeutic agent that is a cationic peptide immunogen comprising a CLT epitope and a T helper cell epitope. Ladd et al. refers to this cationic peptide immunogen as SEQ ID NO: 35. SEQ ID NO: 35 is 100% identical to SEQ ID NO: 9 set forth in the claim. [See result no. 1 of the rag search summary page.] Thus,

SEQ ID NO: 35 of Ladd et al. is a cationic peptide comprising a CTL epitope and a T helper cell epitope, has a net positive charge of +4, and is synthetic peptide immunogen conjugated to a T-helper epitope.

Ladd et al. teaches that the cationic peptide immunogen is useful for regulating infertility and for treating prostatic hyperplasia, androgen-dependent carcinoma, prostatic carcinoma and testicular carcinoma in males. Ladd et al. also teaches that the cationic peptide immunogen is useful for treating endometriosis, benign uterine tumors, recurrent functional ovarian cysts and premenstrual syndrome, and preventing or treatment of estrogen-dependent breast cancer in females. [Abstract]

Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine the teachings of Ladd et al. and Krieg et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to treat prostatic hyperplasia, androgen-dependent carcinoma, prostatic carcinoma and testicular carcinoma in males; and treat endometriosis, benign uterine tumors, recurrent functional ovarian cysts, premenstrual syndrome, and prevents or treats estrogen-dependent breast cancer in females. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because Ladd et al. demonstrates that the immunotherapeutic agent identified as SEQ ID NO: 35 is useful for treating prostatic hyperplasia, androgen-dependent carcinoma, prostatic carcinoma and testicular carcinoma in males; and treating endometriosis, benign uterine tumors, recurrent functional ovarian cysts,

premenstrual syndrome, and prevents or treats estrogen-dependent breast cancer in females.

Regarding the limitation(s) of claims 4 and 6, in addition to teaching a cationic peptide immunogen having the same amino acid as that of SEQ ID NO: 9 recited in the claims, Ladd et al. also teaches the use of a mixture of synthetic peptide immunogens. Specifically, Ladd et al. teaches a mixture comprising the cationic peptide immunogen identified as SEQ ID NO: 35 with SEQ ID NO: 10. [Claim 20 of Ladd et al.] Furthermore, Ladd et al. also suggests the use of one or more peptide immunogens to reduce or suppress LHRH levels in a mammal. [Lines 26-35 of page 30]

Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use a mixture of peptide immunogens. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to obtain an efficient immune response toward the reduction or suppression of LHRH levels in a mammal. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the determination of a workable, optimal or efficient condition is routinely practiced in the art.

Additionally, a mixture of synthetic peptide immunogens having the amino acid sequence of SEQ ID NOs: 10 and 35 would yield a net positive charge of at least +2. SEQ ID NO: 35 has a net positive charge of +4. SEQ ID NO: 10 has a net positive charge of also +4. The average of the two charges is at least +2.

Conclusion

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick J. Nolan can be reached on (571) 272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

/E. M. L./
Primary Examiner, Art Unit 1648